Exogenous Hormone Use: Oral Contraceptives, Postmenopausal Hormone Therapy, and Health Outcomes in the Nurses' Health Study

Shilpa N. Bhupathiraju, PhD, Francine Grodstein, ScD, Meir J. Stampfer, MD, DrPH, Walter C. Willett, MD, DrPH, Frank B. Hu, MD, PhD, and JoAnn E. Manson, MD, DrPH

Objectives. To review the contribution of the Nurses' Health Study (NHS) to our understanding of the complex relationship between exogenous hormones and health outcomes in women.

Methods. We performed a narrative review of the publications of the NHS and NHS II from 1976 to 2016.

Results. Oral contraceptive and postmenopausal hormone use were studied in relation to major health outcomes, including cardiovascular disease and cancer. Current or recent oral contraceptive use is associated with a higher risk of cardiovascular disease (mainly among smokers), melanoma, and breast cancer, and a lower risk of colorectal and ovarian cancer. Although hormone therapy is not indicated primarily for chronic disease prevention, findings from the NHS and a recent analysis of the Women's Health Initiative indicate that younger women who are closer to menopause onset have a more favorable risk–benefit profile than do older women from use of hormone therapy for relief of vasomotor symptoms.

Conclusions. With updated information on hormone use, lifestyle factors, and other variables, the NHS and NHS II continue to contribute to our understanding of the complex relationship between exogenous hormones and health outcomes in women. (*Am J Public Health.* 2016;106:1631–1637. doi:10.2105/AJPH.2016.303349)

Women of childbearing age and those in the postmenopausal period constitute a major proportion of the total population. In 2012, 75.4 million women in the United States were in the reproductive age range of 15 to 50 years,[1] and as of 2010, approximately 64 million women in the United States were postmenopausal.[2] Among fertile women, oral contraceptives (OCs) are among the most effective and popular forms of contraception, with more than 80% of sexually active women aged 15 to 44 years reporting their use.[3] Because of their widespread use as well as numerous case reports of various side effects, the Nurses' Health Study (NHS) was established to gain insights into the long-term health consequences of OC use. In addition, the NHS evaluated health effects of postmenopausal estrogens and combination estrogen and progestogens. Because the NHS recruited women aged 30 to 55 years at baseline in 1976, it could not examine the effects of OC use during early reproductive life. As a result, the NHS II was established to include a cohort of younger women who started using OCs during adolescence or early adulthood.

We have summarized data from the NHS and NHS II on the links of OC and postmenopausal hormone therapy (HT) use with chronic disease risk.

MEASUREMENT OF EXOGENOUS HORMONE USE

The NHS collected detailed information on use of OCs and postmenopausal HT.

Oral Contraceptive Use

In 1976, NHS participants were asked to "indicate intervals of OC use starting from first use and continuing until the present time." These data were continually updated until 1982, when fewer than 500 women reported such use. As the long-term health effects of OC use were not fully resolved at that time, the NHS II was initiated in 1989 to examine these relationships in younger women, aged 24 to 43 years at enrollment, and to examine the effects of newer OC formulations. On the baseline NHS II questionnaire, we asked each woman to report her complete history of OC use. To aid in recall of past OC use, we provided a structured calendar on which women first recorded, for each year of age (beginning at age 13 years or younger), whether they had used OCs for 2 or more months and, if so, whether they had used OCs for 10 or more months at each age.

Participants were given a booklet that contained a detailed coding list of all 227 OC preparations that were ever marketed in the United States up to that time. The list included photographs, names, and pharmacologic contents with separate codes for 21- versus

ABOUT THE AUTHORS

At the time of study, Shilpa N. Bhupathiraju, Meir J. Stampfer, Walter C. Willett, and Frank B. Hu were with the Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA. Francine Grodstein and JoAnn E. Manson were with the Department of Epidemiology, Harvard T. H. Chan School of Public Health.

Correspondence should be sent to Shilpa N. Bhupathiraju, PhD, Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA (e-mail: sbhupath@hsph.harvard.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

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28-day pills with the same pharmacologic formulation and dose and different codes for different pharmacologic formulations and doses sold under the same brand name. For each year, participants were asked to indicate the code of the OC they used at that age. When multiple brands were used at a particular age, participants were asked to choose the brand they used the longest.

The validity and reproducibility of self-reported OC use and hormone composition were evaluated in a random sample of 215 NHS II participants through a detailed telephone interview using a structured life events calendar. Agreement for a history of ever having used OC was high (99%). Reported mean durations of use were highly correlated (Spearman r = 0.94; $P < .001$) and equivalent for both methods (telephone interview = 42.7 months; questionnaire = 44.6 months). In a subset of women for whom OC prescription records were obtained, medical records confirmed the use of an identical or equivalent brand in 75% of intervals of reported use, indicating that self-reported OC histories are acceptably valid in our cohort (related NHS and NHS II publications are available as a supplement to the online version of this article at http://www.ajph.org).

Postmenopausal Hormone Use

In the NHS, women were asked if they had taken HT after menopause and, if so, for how long. Beginning in 1978, information on HT type was obtained. A majority of users of a known type reported using oral conjugated estrogens. The dose of estrogen therapy was first asked for on the 1980 questionnaire. Starting in 1982, we ascertained information on route (oral vs vaginal) and pattern of use (daily vs cyclically). Although the pattern of use was almost exclusively cyclical in the early follow-up period, it transitioned to daily for most women in later years. Information on transdermal estrogen and formulation (e.g., nonconjugated estrogen) was first obtained in 1988.

Data on progestogen dose were first collected in 1988, and most of the progestogen use was medroxyprogesterone acetate. In the NHS II, beginning in 1989, we asked participants if they had ever used postmenopausal HT and, if so, the type of hormone most recently used. Questions about use of postmenopausal HT during the previous 2 years as well as the HT type, dose, route, and pattern of use have been included on each subsequent biennial questionnaire.

ORAL CONTRACEPTIVE USE AND HEALTH OUTCOMES

Since the inception of the NHS, its investigators have generated an extensive body of evidence on the risks and benefits associated with OC use. Importantly, our findings relate not only to the effects of the first- and second-generation OCs used in the NHS, which had estrogen doses between 50 and 150 micrograms, but also to recent OC formulations used in the NHS II, which contain different forms of hormones with much lower estrogen doses (20–35 μg).

Cardiovascular Disease

Data from the NHS and NHS II have contributed substantially to our knowledge of the relationship between OCs and cardiovascular disease (CVD) outcomes (Table 1). In 1980, using NHS data, Rosenberg and others reported an 80% higher risk of myocardial infarction among current OC users (relative risk |RR| = 1.8; 95% confidence interval |CI| = 1.1, 2.9) and a borderline significant risk among nonsmokers without other risk factors (RR = 2.8; 95% CI = 1.0, 7.8). Of note, the risk of myocardial infarction was markedly elevated (RR = 19.0; 95% CI = 4.7, 7.8) among current OC users who were smokers and hypertensive.[4] Subsequently, Stampfer et al.[5] found that past use of OCs had little or no impact on the risk of subsequent CVD (RR = 0.8; 95% CI = 0.6, 1.0), regardless of duration of use or time since last use, suggesting that the excess risk of myocardial infarction with OC use attenuates quickly upon their discontinuation.

Because the underlying cause of myocardial infarctions in OC users is thrombotic and not atherosclerotic, Grodstein et al.[6] examined the relation between OC use and the risk of pulmonary embolism in the NHS and found that current use was associated with a 2 times risk of primary pulmonary embolism (RR = 2.2; 95% CI = 0.8, 5.9) although this estimate was determined by 5 events among current OC users. Past use was not associated with a higher risk (RR = 0.8; 95% CI = 0.5, 1.2). OC use has also been associated with incident hypertension. In the NHS II, current users of OCs had an 80% higher risk of hypertension (RR = 1.8; 95% CI = 1.5, 2.3) compared with women who had never used them. Again, risk attenuated quickly on cessation of use (RR = 1.2; 95% CI = 1.0, 1.4).[17] Conversely, OC use within 2 years of pregnancy was associated with a subsequently lower risk of gestational hypertension (RR = 0.7; 95% CI = 0.4, 1.0).[7]

Consistent with the literature, our findings indicate that current OC use is associated with a higher risk of CVD, primarily among women with risk factors such as smoking and hypertension. Because of the low absolute risks of CVD among generally healthy and nonsmoking women of reproductive age, OCs remain an appropriate choice to prevent unwanted pregnancy.

Cancer

Current OC use appears to be associated with a higher risk of invasive breast cancer, although risk differs by age and hormone formulation (Table 1). In the first prospective NHS investigation of OC and breast cancer, premenopausal women who were current OC users had a 50% higher risk of breast cancer (95% CI = 1.0, 2.3) although past use was not associated with risk (RR = 1.0; 95% CI = 0.8, 1.3).[8] Among older women (older than 40 years) in the NHS, use of OC for 10 or more years and past OC use before a first full-term pregnancy was not significantly associated with breast cancer risk.[9] When examining formulations prescribed in the 1990s in the younger NHS II cohort, current OC use was found to be associated with a 33% higher risk (95% CI = 3%, 73%) of breast cancer. Triphasic preparations with levonorgestrel substantially accounted for the higher risk (RR = 3.05; 95% CI = 2.00, 4.66). However, a higher risk was not observed among past users (RR = 1.12; 95% CI = 0.95, 1.33).[10]

Unlike for breast cancer, for ovarian cancer a lower risk was associated with OC use with increasing duration of use (RR for > 10 years = 0.62; 95% CI = 0.37, 1.04; P-trend = 0.02).[11] Also, in a combined analysis with other cohorts, this association was stronger for rapidly fatal ovarian cancer (RR per 5-year increase = 0.69; 95% CI = 0.58,

TABLE 1—Oral Contraceptive Use and Risk of Cardiovascular Disease and Cancer: NHS and NHS II, United States, 1976–2016

Outcome	Population	Summary of Findings
Cardiovascular disease		
Myocardial infarction	NHS	Increased myocardial infarction risk overall and elevated risk among nonsmokers without other risk factors[4]
Total cardiovascular disease	NHS 1976–1984	Risk of subsequent CVD not materially raised with past OC use[5]
Pulmonary embolism	NHS 1976–1992	Risk higher with current use of OCs but not with past use[6]
Gestational hypertension, preeclampsia	NHS II 1991–1995	Recent OC use associated with lower risk of developing gestational hypertension with a suggestion of higher risk of developing preeclampsia[7]
Cancer		
Breast cancer	NHS 1976–1980	Ever use of OC not associated with higher risk of breast cancer; among premenopausal women, current OC use associated with higher risk[8]
Breast cancer	NHS 1976–1992	No appreciable increase in breast cancer risk in women older than 40 y with long-term past OC use, either overall or before a first full-term pregnancy[9]
Breast cancer	NHS II 1989–2001	Excessive risk of breast cancer with current use of OCs; levonorgestrel used in triphasic preparations may account for much of this higher risk[10]
Invasive epithelial ovarian cancer	NHS 1976–2004	Duration of OC use appears to be inversely associated with risk[11]
Epithelial ovarian cancer	NHS	Every 5-y increase in OC use associated with a lower risk of rapidly fatal ovarian cancer and less aggressive ovarian cancer[12]
Colorectal cancer	NHS 1980–1992	Lower risk of colorectal cancer with a significant inverse trend for longer duration of use[13]
Adenomatous polyps of the distal colorectum	NHS 1980–1994	Ever OC use not associated with development of adenomatous polyps of the distal colorectum or the distal colon[14]
Colorectal cancer	NHS 1980–2010; NHS II 1991–2009	No association with colorectal cancer risk in NHS or NHS II[15]
Melanoma	NHS 1976–1994; NHS II 1989–1995	Risk of premenopausal melanoma higher among current OC users and among those with longer duration of use[16]

Note. CVD = cardiovascular disease; NHS = Nurses' Health Study; OC = oral contraceptive.

0.82) than for less aggressive disease (RR = 0.81; 95% CI = 0.74, 0.89).[12]

Ever use of OC was associated with a nonsignificantly lower risk of colorectal cancer (RR = 0.84; 95% CI = 0.69, 1.02) in the NHS, with risk being substantially lower with increasing duration of use (RR for > 95 months = 0.60; 95% CI = 0.40, 0.89; P-trend = 0.02).[13] Yet, ever OC use had no relation to development of adenomatous polyps of the distal colorectum (RR = 1.0; 95% CI = 0.8, 1.1).[14] Most recently, with extended follow-up (30 years in the NHS and 20 years in the NHS II), Charlton et al.[15] found that ever OC use was not associated with lower colorectal cancer in the NHS (RR = 1.01; 95% CI = 0.91, 1.12) and the NHS II (RR = 1.03; 95% CI = 0.69, 1.53), suggesting that the inverse relation with long-term recent use attenuates over time. Still, among the NHS II women with 5 or more years of OC use, an inverse association was seen with cancers of the colon (hazard ratio |HR| = 0.61; 95% CI = 0.38, 0.99), especially the proximal colon (HR = 0.51; 95% CI = 0.26, 1.00).

Current OC use was found to be associated with a 2 times higher risk of melanoma (RR = 2.0; 95% CI = 1.2, 3.4), with highest risk among current users with 10 or more years of use (RR = 3.4; 95% CI = 1.7, 7.0). Risk disappeared on discontinuation (RR for past use < 5 years = 1.0; 95% CI = 0.8, 1.5).[16] No associations were documented between duration of OC use and the risk of bladder[18] and renal cancers.[19]

Epidemiological evidence from the NHS suggests that the effects of OC use on cancer are mixed, with a higher risk seen for melanoma and breast cancer and a lower risk for colorectal and ovarian cancers.

Mortality

Over a 36-year follow-up period in the NHS, OC use was not associated with all-cause mortality (HR = 1.02; 95% CI = 0.99, 1.04) although longer duration of use (≥ 10 years) was associated with a higher risk of death from breast cancer (HR = 1.39; 95% CI = 1.13, 1.71) and a lower risk of death from ovarian cancer (HR = 0.60; 95% CI = 0.40, 0.93).

Ever use of OCs was not associated with CVD mortality (HR = 1.00; 95% CI = 0.94, 1.06) or ischemic heart disease mortality (HR = 1.04; 95% CI = 0.95, 1.14).[20]

Other Clinical Endpoints

In studies of other outcomes, in the NHS and NHS II, current and past OC use was associated with a higher risk for Crohn's disease although a higher risk of ulcerative colitis was seen only among women with a history of smoking.[21]

Ever use of OCs was associated with a higher risk of systemic lupus erythematosus.[22] Conversely, OC use was not associated with risk for type 2 diabetes, multiple sclerosis, rheumatoid arthritis, or Parkinson's disease.

POSTMENOPAUSAL HORMONE USE AND HEALTH OUTCOMES

Estrogen therapy has been used to treat vasomotor symptoms since the 1940s and was one of the most frequently prescribed treatments in the United States by the 1970s. With its widespread use, it was imperative to understand the long-term effects of postmenopausal HT on various health outcomes. The NHS is one of the largest cohort studies to have comprehensive information on HT use over 4 decades. Indeed, much of the evidence on HT and chronic disease leading up to the start of the Women's Health Initiative (WHI) originated from the NHS. In this section, we review updated findings on HT and health outcomes.

Cardiovascular Disease

CVD remains the leading cause of death in women aged 65 years or older. However, CVD mortality rates among younger women are distinctly lower than are those among men, leading many to believe that endogenous hormones among premenopausal women offer a cardioprotective benefit that is lost with menopause. In one of the earliest prospective investigations, current HT use was associated with a 70% lower risk (95% CI = 36%, 86%) of total coronary heart disease (CHD) and a 66% lower risk (95% CI = 18%, 86%) of nonfatal myocardial infarction (Table 2).[23] Subsequent analyses with longer durations of follow-up supported a protective association of current estrogen use with CHD.[36,37] In addition to a lower risk of a first event, current use of estrogen for 2 or more years was associated with a lower risk of recurrent major coronary events (RR = 0.38; 95% CI = 0.22, 0.66) although short-term use (< 1 year) was associated with a pattern of higher risk (RR = 1.25; 95% CI = 0.78, 2.00).[26]

Because of the growing evidence for lower rates of CHD among women using HT,[38] the WHI was launched in 1992 to examine the effects of HT on CVD and other health outcomes among postmenopausal women aged 50 to 79 years in 2 separate randomized controlled trials. However, both arms of the WHI trial were stopped earlier than planned because of risks outweighing benefits in the estrogen plus progestin trial[39] and an increased risk of stroke with the use of conjugated equine estrogens.[40] In light of these results, 2 separate articles examined the potential reasons for the divergent findings.

Grodstein et al.[25] found that time since menopause and age at HT initiation modified the relationship between HT use and CVD risk. The apparent protective effect of HT use on CVD risk was seen only in women who initiated HT near menopause (defined as < 4 years since menopause onset), with no evidence of a lower risk among those who initiated such therapy 10 or more years after menopause. In another analysis, the NHS data were used to simulate the design and intention-to-treat analysis of the WHI. The discrepancies between the 2 studies could largely be explained by differences in the distribution of time since menopause and length of follow-up.[41] Specifically, in the WHI, most of the women were randomized to HT or placebo many years after menopause (median age = 63 years) and, as found in the Grodstein analysis, no benefit was seen (HR = 0.96; 95% CI = 0.78, 1.18).

Despite the divergent findings for CHD, results were remarkably similar between observational studies like the NHS and clinical trials like the WHI for other outcomes such as stroke, breast cancer, and hip fracture. The discordant findings can potentially be explained by differences in methodology, such as residual confounding, compliance bias, or incomplete capture of early clinical events, or in biology, such as hormone formulation and dose, endogenous estrogen concentrations, time since menopause, or stage of atherosclerosis.[42] For example, a majority of women in the NHS initiated HT closer to menopause onset and at a much younger age than did their WHI counterparts.

Similar to the WHI findings, in the NHS, current use of estrogen alone (RR = 1.39; 95% CI = 1.18, 1.63) or with progestin (RR = 1.27; 95% CI = 1.04, 1.56) was associated with a higher risk of stroke over a 24-year period, and this risk did not appear to be related to the timing of HT initiation.[25] Likewise, in the NHS, over a 16-year period, current HT use was associated with a 2 times higher risk of primary pulmonary embolism (RR = 2.1; 95% CI = 1.2, 3.8) although past use showed no association with risk (RR = 1.3; 95% CI = 0.7, 2.4).[6]

Cancer

The NHS cohorts have generated a wealth of evidence on HT and cancer risk (Table 2). Our findings show that current use of HT is associated with a higher risk of breast cancer[27] and that this risk increases with longer duration of use.[27–29] When examining specific HT formulations, similar to the findings of the intervention phase of the WHI (median follow-up = 6.8 years; RR = 0.79; 95% CI = 0.61, 1.02),[40] current use of unopposed estrogen therapy use for 5.0 to 9.9 years was not associated with a higher risk of breast cancer in the NHS (RR = 0.87; 95% CI = 0.71, 1.07) among postmenopausal women who underwent a hysterectomy.

However, longer duration of use, which could not be examined in the WHI, was associated with a trend toward higher risk: use for 20 or more years was associated with a 42% higher risk of breast cancer (RR = 1.42; 95% CI = 1.13, 1.77), especially for cancers positive for estrogen receptor and for progesterone receptor (RR = 1.73; 95% CI = 1.24, 2.43).[28] As in the WHI, in the NHS, current use of estrogen plus progestin was associated with a higher risk of invasive breast cancer (RR = 1.66; 95% CI = 1.49, 1.89).[30] The NHS cohort was also one of the first to quantify the relationship between other types of HT formulations and breast cancer risk.

Over 14 years of follow-up (1978–1992), the use of estrogens (other than conjugated estrogens) or progestins alone was associated with multivariable adjusted RRs for breast cancer of 1.28 (95% CI = 0.97, 1.71) and 2.24 (95% CI = 1.26, 3.98), respectively.[29] In another article with 10 additional years of follow-up, the risk of breast cancer was found to be nearly 2.5 times higher (RR = 2.48; 95% CI = 1.53, 4.04) among current users of estrogen plus testosterone than among never users.[30] Taken together, evidence from the NHS indicates that HT is associated with a higher risk of breast cancer, especially with long-term use, and with positive for estrogen receptor and positive for progesterone receptor cancers.

We also reported on the association of HT use with other cancers. Those who used unopposed estrogen (RR per 5-year increment of use = 1.25; 95% CI = 1.12, 1.38) but not estrogen plus progestin (RR per

TABLE 2—Postmenopausal Hormone Use and Risk of Cardiovascular Disease and Cancer: NHS and NHS II, United States, 1976–2016

Outcome	Exposure or Hormone Formulation	Population	Summary of Findings
Cardiovascular disease			
CHD	Estrogen Estrogen + progestin	NHS 1976–2000	Initiation of HT near menopause (< 4 y since onset) associated with lower CHD risk; initiation of HT ≥ 10 y after menopause onset not associated CHD risk; current use of estrogen + progestin not associated with risk[24]
Stroke	Estrogen Estrogen + progestin	NHS 1976–2004	Use associated with higher risk that does not appear to be related to timing of HT initiation[25]
Recurrent CHD	Current postmenopausal HT use	NHS women with previous myocardial infarction or atherosclerosis 1976–1996	Short-term use appears to be associated with higher risk of recurrent major coronary events; longer-term use associated with lower risk[26]
Pulmonary embolism	Postmenopausal HT use	NHS 1976–1992	Current but not past HT use associated with higher risk[6]
Cancer			
Invasive breast cancer	Current HT use	NHS 1980–1996	Higher risk of breast cancer[27]
Invasive breast cancer	Conjugated equine estrogens	NHS 1980–2002	Use associated with higher risk of breast cancer but only after longer-term use and only for estrogen receptor and progesterone receptor cancers[28]
Invasive breast cancer	HT use	NHS 1976–1992	Use of conjugated estrogens alone or with progestins associated with higher risk[29]
Invasive breast cancer	Estrogen + testosterone	NHS 1978–2002	Higher risk with use of testosterone alone or with estrogen[30]
Ovarian cancer	Estrogen Estrogen + progestin	NHS 1976–2002	Use of unopposed estrogen, but not estrogen plus progestin, associated with significantly higher epithelial ovarian cancer risk[31]
Endometrial cancer	Estrogen Estrogen + progesterone	NHS 1976–2004	Long-term use (≥ 5 y) of estrogen and combined estrogen plus progesterone associated with higher risk[32]
Colorectal cancer	Postmenopausal HT use	NHS 1980–1994	Current use associated with lower risk but apparent lowering of risk disappeared on cessation[33]
Colorectal cancer	Postmenopausal HT use	NHS 1980–2006	Current HT use associated with lower risk for CDKN1A-nonexpressed but not for CDKN1A-expressed tumors[34]
Lung cancer	Postmenopausal HT use	NHS 1984–2006	HT may influence lung carcinogenesis although association is likely modest and altered by smoking status[35]
Renal cell cancer	Postmenopausal HT use	NHS 1976–2004	Current use of estrogen alone or with progesterone not associated with risk[19]
Bladder cancer	Postmenopausal HT use	NHS 1976–2002	Current use of estrogen or with progestin not associated with bladder cancer risk[18]

Note. CHD = Coronary heart disease; HT = hormone therapy; NHS = Nurses' Health Study.

5-year increment of use = 1.04; 95% CI = 0.82, 1.32) had a higher risk of epithelial ovarian cancer than did never users.[31] Likewise, long-term (≥ 5 years) use of estrogen alone (RR = 7.67; 95% CI = 5.57, 10.57) and with progestin (RR = 1.52; 95% CI = 1.03, 2.23) was associated with endometrial cancer risk.[32] Conversely, current HT use was associated with a 35% (95% CI = 17%, 50%) lower risk of colorectal cancer, although this did not persist after discontinuation of HT use.[33]

In a more recent analysis, with 26 years of follow-up, Lin et al.[34] noted that the association between current HT use and colorectal cancer risk differed by expression of the cell cycle–related tumor biomarker CDKN1A; a lower risk with current HT use was observed with CDKN1A-nonexpressed tumors but not CDKN1A-expressed tumors. There was no evidence for an association between HT use and the risk of lung cancer,[35] renal cell cancer,[23] or bladder cancer.[18]

Mortality

The NHS analyses have shown that current HT use is associated with a lower mortality risk (RR = 0.63; 95% CI = 0.56, 0.70) although this apparent benefit was attenuated with long-term use (RR = 0.80; 95% CI = 0.67, 0.96). Death from CHD was seen to markedly decrease with HT use (RR = 0.47; 95% CI = 0.32, 0.69), and no overall association for death from breast cancer (RR = 0.76; 95% CI = 0.56, 1.02) with HT use was seen.[43]

Additionally, among those with colorectal cancer, estrogen use before colorectal cancer diagnosis was associated with a lower risk of colorectal cancer–specific mortality (HR = 0.64; 95% CI = 0.47, 0.88).[44]

Other Clinical Endpoints

Because of the plausibility for a biological role of estrogen on various comorbidities, several investigators have harnessed the resources of the NHS to examine associations between HT and other clinical outcomes. The NHS was the first cohort to show that postmenopausal estrogen therapy was associated with a lower risk of type 2 diabetes, although this lower risk did not persist among past users.[45] Conversely, past or current HT use has been shown to be associated with higher rates of cognitive decline in older women, especially among those with an APOE e4 allele. HT use was also associated with a higher risk of ulcerative colitis, systemic lupus erythematosus, and urinary incontinence; a greater likelihood of gastroesophageal reflux disease; a lower risk of gout; and no overall association with incident kidney stones. Finally, postmenopausal HT use was associated with a lower risk of hip fracture among women with low levels of physical activity (i.e., < 3 metabolic equivalent of task–hours per week).

Taken together, the findings from the NHS and the WHI trials indicate that HT use for chronic disease reduction is not warranted. However, HT continues to have an important clinical role in the management of menopausal symptoms, and it is possible to identify a subset of women (e.g., younger women and those who are closer to menopause onset) who have a more favorable risk–benefit profile.

LESSONS LEARNED

Although much has been learned from the NHS cohorts, our findings need to be placed in the context of a few limitations that are inherent to observational studies. For example, hormone users are a self-selected group and usually have healthier lifestyles than do nonusers. The NHS investigators addressed this by adjusting for these factors in all analyses. Differences in surveillance for clinical outcomes, such as higher rates of screening mammography in HT users than in nonusers, may introduce confounding and cannot be excluded in observational studies.

Finally, our findings may have limited generalizability because of the homogeneity of our population with regard to race, education, and income. Yet, the high educational status of our study participants may be advantageous because reliable and valid data can be captured. The cohorts have made substantive contributions to our understanding of the balance of benefits and risks of exogenous hormones and have generated numerous hypotheses for testing in randomized controlled trials. AJPH

CONTRIBUTORS

S. N. Bhupathiraju reviewed the literature and drafted and revised the article. S. N. Bhupathiraju and J. E. Manson conceptualized and oversaw the project. F. Grodstein, M. J. Stampfer, W. C. Willett, F. B. Hu, and J. E. Manson critically revised the article for important intellectual content.

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HUMAN PARTICIPANT PROTECTION

Institutional review board approval was not needed for this review because no human participants were involved.

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EDITOR'S NOTE

Because of space restrictions and the large volume of references relevant to the Nurses' Health Study, additional references are provided in a supplement to the online version of this article at http://www.ajph.org.